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The Effects of Erdosteine on Tracheal Healing in Rats

Wpływ erdosteiny na gojenie tchawicy u szczurów

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Abstract

Background. Proliferating scar tissue and strictures, which are still serious problems of tracheal surgery, are caused by an inflammatory reaction with subsequent edema and granulation tissue. Tracheal stenosis leads to severe morbidity and multiple surgical operations are sometimes needed in those patients.
Objectives. To assess the effect of the antioxidant and anti-inflammatory drug Erdosteine to prevent tracheal stenosis in a rat model.
Material and Methods. Fourteen female adult Wistar albino rats were divided into two groups, a control group (Group A, n = 7) and an Erdosteine group (Group B, n = 7). Under general anesthesia, the tracheas were incised vertically, extending from the 3rd to the 5th cartilaginous rings and closed primarily with absorbable sutures. Group A had 0.5 cc/day 0.9% NaCl, and Group B had 10 mg/kg/day Erdosteine, both administered by gavages and maintained for 10 days. At the end of the procedure, the rats were sacrificed and their tracheas were excised from cricoid cartilage to carina. The specimens were histologically evaluated using light microscopy and scored for inflammatory cell infiltration, angiogenesis, fibroblast proliferation, collagen deposition, and epithelial regeneration. All of the results were statistically analyzed and a value of $p < 0.05$ was considered statistically significant.
Results. There were only meaningful differences in epithelial regeneration ($p = 0.001$), displaying that epithelial regeneration was better in Group B. However, the differences in inflammatory cell infiltration, angiogenesis, fibroblast proliferation and collagen deposition did not reach statistical significance.
Conclusions. The severity of pathological changes forming in the tissue after tracheal surgery could not be reduced with Erdosteine use. Thus, Erdosteine does not seem to be an applicable preventive treatment agent for possible postsurgical tracheal stenosis (**Adv Clin Exp Med 2011, 20, 1, 31–37**).

Key words: trachea; thoracic surgery, inflammation, wound healing, tracheal stenosis, agents, anti-inflammatory.

Streszczenie

Wprowadzenie. Bliznowacenie i zwężenia, które wciąż pozostają poważnym problemem w chirurgii tchawicy, są wywołane przez reakcję zapalną z obrzękiem i powstawaniem ziarniny. Zwężenie tchawicy prowadzi do ciężkich powikłań i często jest związane z koniecznością licznych interwencji chirurgicznych.
Cel pracy. Ocena antyoksydacyjnego i przeciwzapalnego leku erdosteiny w zapobieganiu zwężenia tchawicy na modelu szczurzym.
Materiał i metody. Czternaście dorosłych szczurów Wistar albino płci żeńskiej podzielono na dwie grupy: grupę kontrolną (grupa A, n = 7) i grupę erdosteiny (grupa B, n = 7). W znieczuleniu ogólnym przeprowadzono nacięcie tchawicy rozciągające się od trzeciej do piątej chrząstki, które zamknięto z użyciem szwów wchłaniających się. Grupa A otrzymała 0,5 cc/dzień 0,9% NaCl, a grupa B 10 mg/kg/dzień erdosteiny, obie substancje podawano przez 10 dni. Na zakończenie zabiegu szczury zostały zabite, a ich tchawice wycięte od chrząstki pierścieniowatej do ostrogi. Materiał badano histologicznie z zastosowaniem mikroskopu świetlnego i oceniano naciek komórkami zapalnymi, angiogenezę, proliferację fibroblastów, złogi kolagenu i regenerację nabłonka. Uzyskane wyniki poddano analizie statystycznej, a wartość $p < 0,05$ przyjęto za istotną statystycznie.

Wyniki. Stwierdzono tylko jedną istotną różnicę w regeneracji nabłonka (p = 0,001), przemawiającą za tym, że regeneracja nabłonka była lepsza w grupie B. Różnice w nacieku komórek zapalnych, angiogenezie, proliferacji fibroblastów i złogach kolagenu nie były jednak istotne statystycznie.
Wnioski. Zastosowanie erdosteiny nie zmniejszało ciężkości zmian patologicznych powstających w tkance po chirurgii tchawicy, dlatego nie wydaje się, aby zastosowanie erdosteiny mogło zapobiegać pooperacyjnym zwężeniom tchawicy (**Adv Clin Exp Med 2011, 20, 1, 31–37**).

Słowa kluczowe: tchawica, torakochirurgia, zapalenie, gojenie ran, zwężenie tchawicy, czynniki przeciwzapalne.

Tracheal healing is a distressed condition and this process results in fibrosis and collagen deposition in the surgical region. Sometimes excessive collagen accumulation and fibroblast proliferation may cause narrowing in the lumen of trachea and tracheal stenosis may occur. Generally, this stenosis develops after tracheal surgery or prolonged endotracheal intubations and it is a diagnostic and therapeutic problem in surgical practice [1, 2].

As is known, the wound healing process is comprised of a continuous sequence of inflammation, proliferation and maturation. Epithelial, endothelial, inflammatory cells and fibroblasts briefly come together and interact to restore the injured tissue. At the end of these phases, collagen synthesis and scar tissue formation occurs [1]. Patients with poor wound healing develop poor epithelial closure and increased granulation tissue. However, tracheal stenosis formation begins with mucosal edema and ulceration, which are often associated with local infection on the healing tracheal wound. Afterward, perichondritis and chondritis can damage tracheal annuli cartilage. Secondary healing of the ulceration, necrosis, and infection produces granulation tissue. Then, increased fibroblastic activity generates retractile fibrous tissue that causes stenosis with smaller diameter of trachea and airway obstruction [2].

Considering the inflammatory cause of this process, we thought that antioxidant and anti-inflammatory drugs may prevent or diminish stenosis after tracheal surgery, and have designed the current study in which Erdosteine was used after a tracheal surgery in rats.

Material and Methods

Population

A prospective, randomized, double-blinded, controlled study was conducted with fourteen female adult Wistar albino rats from the same colony, each weighing 220-250g. Rats were used due to their easy availability, safety and the high ratio of repeating the experiment.

Design

The rats were divided into two groups at random. 1 – Group A: Control (n = 7), 2 – Group B: Erdosteine (n = 7). The animals were kept in a light-controlled room with a 12:12-h light–dark cycle; temperature (22 ± 0.5°C) and relative humidity (65–70%) were kept constant. Food and water were available ad libitum. They had not been used in another study, and they had not been given any drugs previously. The rats were deprived of food for 12 h before the experiment, but had free access to water. All rats were anesthetized by administering ketamine hydrochloride (Ketalar, Pfizer, Turkey) 50 mg/kg and xylazine hydrochloride (Rompun, Bayer, Turkey) 3 mg/kg through intraperitoneal injection. During the operations, additional doses were applied if necessary. Experiments were carried out under sterile conditions. During surgery, to prevent the effects of hypothermia and to provide the stability of hemodynamic parameters, the body temperature was maintained at 37.0°C with the use of a heating pad.

The rats were placed in supine position. A vertical midline cervical incision was performed and strap muscles were retracted laterally. After the exposure of the trachea, a vertical incision on the anterior tracheal wall including the 3rd to 5th cartilaginous rings was made and then closed primarily with the interrupted suture technique by using 4/0 absorbable (polyglactine) sutures. Then, the layers were closed properly after bleeding control. Antibiotic therapy with cefazolin sodium (15 mg/kg/intramuscular) was given for 10 days. In the first 24 hours, rats were given Buprenorphine 0.03 mg/kg every 8 hours subcutaneously. They were kept in different cages, and were given food and water as much as they wanted.

Group A had 0.5 cc/day 0.9% NaCl, and Group B had 10 mg/kg/day Erdosteine (Erdostin, Sandoz, Turkey) by gavages, which was maintained for 10 days beginning from the day of the operation. The rats were sacrificed at the end of the 10th day by administering lethal ketamine hydrochloride intraperitoneally. The tracheas were excised from cricoid cartilage to carina with adjacent esophagus. The specimens were promptly fixed in 10% formalin, processed for paraffin embedding, and a horizontal cross section at 5 μm. of the middle part of the incised trachea was performed. Then, Hematoxylin-Eosin stained sections were used to evaluate histopathological findings by light microscopy. One blinded pathologist analyzed the samples.

The Ehrlich/Hunt numeric scale was used for scoring of inflammatory cell infiltration, angiogenesis, fibroblast proliferation and collagen deposition [3]. The scores were 0 for absence, 1 for occasional presence, 2 for light scattering, 3 for abundance and 4 for confluence of cells or fibers. Epithelial regeneration was evaluated according to the scoring in a Loewen's study [4]. The scores were 0 for no epithelium, 1 for single-layer epithelium with partial closure, 2 for multi-layer epithelium with complete closure for airway healing.

Ethics

This study began after approval by a local ethics board in the Duzce University Faculty of Medicine, Experimental Animals Laboratory, in 2009. The rats were cared for in accordance with the Guide for the Care and Use of Laboratory Animals.

Statistical Analysis

The statistical analysis was performed with SPSS software, version 11.5 (SPSS, Inc., Chicago, IL). Clinical data were expressed as the median ± the standard Error of Mean (Minimum-maximum). A Mann-Whitney *U*-test was used for group comparison and a p value less than 0.05 was considered as statistically significant.

Results

All the rats survived the surgical procedure and the study time. Wound infection occurred in one rat (in Group A), so it was excluded from the experiment protocol. Instead of this rat, a new experimental subject was added to this group. In the other rats neither infection nor complication was observed.

Macroscopic examination of the incised trachea region was more rigid and thick than non-incised normal trachea in all specimens of both groups. However, these tracheas did not reveal obstruction of the lumen in the operated area or any dehiscence on the suture line.

The specimens were histologically evaluated and scored for inflammatory cell infiltration, angiogenesis, fibroblast proliferation, collagen deposition, and epithelial regeneration. The results are present in Table 1.

When preparations from Group A were examined, it was observed that in the trachea, a dense inflammatory cell and especially lymphocyte infiltration was present at the surgical area, in addition to this, angiogenesis and fibroblast proliferation had increased in these areas. However, collagen deposition was not encountered besides the normal collagen tissue, and a slight increase in epithelial regeneration was determined. In general, tissue loss has been determined in the epithelial tissue, in

Table 1. The histopathological scores of Group A and Group B

Tabela 1. Ocena histopatologiczna grupy A i grupy B

Rat No (Numer szczura)	Inflammatory cell infiltration (Naciek zapalny komórek)	Angiogenesis (Angiogeneza)	Fibroblast proliferation (Proliferacja fibroblastów)	Collagen deposition (Zawartość kolagenu)	Epithelial regeneration (Regeneracja nabłonka)
Group A-1	3	3	3	0	0
Group A-2	3	3	3	0	0
Group A-3	2	2	2	0	1
Group A-4	2	1	1	0	1
Group A-5	1	1	1	0	1
Group A-6	1	1	1	0	0
Group A-7	1	1	1	0	1
Group B-1	2	1	2	1	2
Group B-2	2	0	1	0	2
Group B-3	3	3	3	0	2
Group B-4	1	1	1	1	2
Group B-5	1	0	1	0	2
Group B-6	2	1	0	0	2
Group B-7	2	1	1	0	2

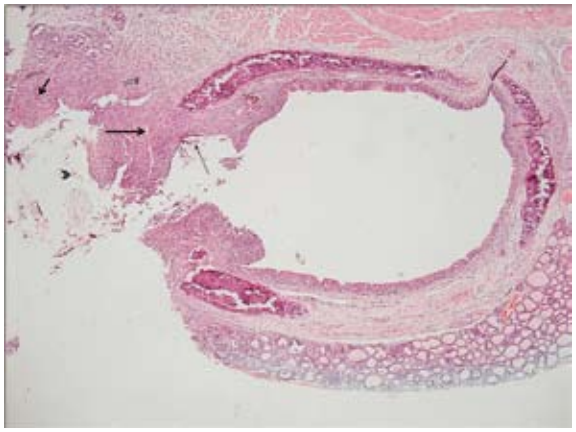

Fig. 1. Photomicrograph of histopathology from Group A (Control) displaying increased inflammatory cell infiltration (short-thin arrow), angiogenesis (short-thick arrow), and fibroblast proliferation (long-thick arrow). However, a significant collagen deposition (double arrow) was not encountered. Overall, tissue loss was observed in the epithelial tissue near the suture area, and a partial increase in epithelial regeneration was discovered (long-thin arrow). (Arrow head: foreign body – suture materials) (Hematoxylin-Eosin, original magnification ×4)

Ryc. 1. Mikrofotografia wycinka histopatologicznego z grupy A (grupa kontrolna), która przedstawia wzrost komórek nacieku zapalnego (krótka cienka strzałka), angiogenezę (krótka gruba strzałka) i proliferację fibroblastów (długa gruba strzałka). Nie wykryto jednak znacznego odkładania się kolagenu (podwójna strzałka). Ogólnie rzecz biorąc, utratę tkanki zaobserwowano w tkance nabłonkowej w pobliżu strefy szwu oraz częściowe przyspieszenie regeneracji nabłonka (długa cienka strzałka) (grot strzałki: ciało obce – materiał do wykonania szwu) (HE, oryginalne powiększenie 4×)

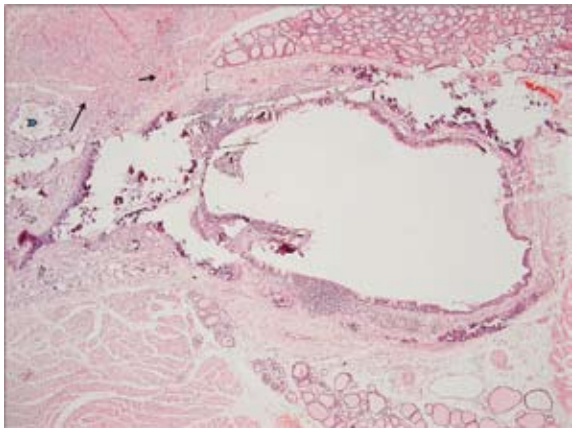

Fig. 2. Photomicrograph of histopathology from Group B (Erdosteine) displaying increased inflammatory cell infiltration (short-thin arrow), angiogenesis (short-thick arrow), and fibroblast proliferation (long-thick arrow). However, a significant collagen deposition (double arrow) was not encountered. Overall, epithelial regeneration was increased, and major tissue defects were not observed in the epithelium (long-thin arrow). (Arrow head: foreign body – suture materials) (Hematoxylin-Eosin, original magnification ×4)

Ryc. 2. Mikrofotografia wycinka histopatologicznego z grupy B (Erdosteina), która przedstawia wzrost komórek nacieku zapalnego (krótka cienka strzałka), angiogenezę (krótka gruba strzałka) i proliferację fibroblastów (długa gruba strzałka. Nie wykryto jednak znacznego odkładania się kolagenu (podwójna strzałka). Ogólnie rzecz biorąc, regeneracja nabłonka zwiększyła się, w nabłonku nie stwierdzono większych uszkodzeń tkanki (długa cienka strzałka) (grot strzałki: ciało obce – materiał do wykonania szwu) (HE, oryginalne powiększenie 4×)

areas near the suture region. When preparations from Group B were examined, in the operated area of the trachea and especially in subepithelial regions, a dense inflammatory cell infiltration, dominantly consisting of lymphocytes and increased angiogenesis was observed. An increased fibroblast proliferation was observed in this area; however, no significant collagen deposition was encountered. Overall, epithelial regeneration in this group increased and no major tissue defect was observed in the epithelium. Histopathological photographs of section are shown in Figs. 1-2.

All of the histopathological results were statistically analyzed for significance. There were only meaningful differences in epithelial regeneration ($p = 0.001$), showing that epithelial regeneration was better in Group B. However, the differences in inflammatory cell infiltration, angiogenesis, fibroblast proliferation and collagen deposition did not reach the statistical significance (Table 2).

Table 2. The results of statistical analysis (median ± SEM)

Tabela 2. Wyniki analizy statystycznej (mediana ± SEM)

Parameter (Wskaźnik)	Group A Control (n = 7)	Group B Erdosteine (n = 7)
Inflammatory cell infiltration (Naciek zapalny komórek)	2.00 ± 0.34	2.00 ± 0.26
Angiogenesis (Angiogeneza)	1.00 ± 0.36	1.00 ± 0.38
Fibroblast proliferation (Proliferacja fibroblastów)	1.00 ± 0.36	1.00 ± 0.36
Collagen deposition (Zawartość kolagenu)	0.00 ± 0.00	0.00 ± 0.18
Epithelial regeneration (Regeneracja nabłonka)	1.00 ± 0.20	2.00 ± 0.00

Discussion

This study underlines three points: (a) In the experimental tracheal surgery model, the anti-inflammatory effect expected by the use of Erdosteine could not be obtained and when inflammatory cell infiltration, angiogenesis and fibroblast proliferation in the surgical area were examined histopathologically, similar results to those with the control group were obtained. (b) Erdosteine did not affect the collagen deposition amount in the surgical area. (c) In the group that was given Erdosteine, an overall increase of epithelial regeneration was observed in the surgical area.

In general, after tracheal surgery, the wound healing process starts in the suture line and inflammatory reaction forms in this area during the early period. Through the migration of inflammatory cells such as macrophage, neutrophil and lymphocytes, platelets, fibroblasts, and epithelial cells come together forming the inflammatory reaction, and they start repairing the injured tissue. However, free oxygen radicals (H_2O_2, O_2^-, OH^-) and proteases released from accumulated inflammatory cells and especially neutrophils, at the same time damage cellular components, causing microvascular leakage and lipid peroxidation of cellular membranes which in turn generate more free radicals in a self-propagating cycle leading to pathological changes from edema and cell injury to cell death by necrosis.

The tissue damage triggered by oxidative stress and increased fibroblastic activity generate retractile fibrous tissue that causes tracheal stenosis. Some studies where various drugs were used have searched for a way to modulate the tracheal healing process in order to prevent stenosis after tracheal surgery. In their experimental study, Talas et al performed tracheal transections and primary anastomoses on rats and have found that dexamethasone significantly impairs the healing of tracheal anastomoses, and postoperative administration of vitamin A reverses this inhibitory effect [5]. In their study where Olmos-Zuniga et al performed cervical tracheal resection and tracheoplasty on dogs, and they topically applied a modulator of the fibrogenesis, hyaluronic acid, to the tracheal anastomose area. The authors examined tracheal healing macroscopically and microscopically and, as a result, they state that hyaluronic acid reduces postsurgical tracheal stenosis and inflammation, as well as improves the quality of the tracheal healing [6]. Liman et al. studied the effects of estradiol and progesterone, and found that these hormones inhibit massive collagen accumulation and fibroblast proliferation in tracheal healing and concluded that they may prevent tracheal stenosis [1]. In addition, hyperbaric oxygen therapy and heparin have been used for prevention of tracheal stenosis in experimental animal studies and positive results were obtained [7, 8].

In this study, our goal was to prevent scar formation and tracheal stenosis development by using Erdosteine, a drug that has anti-inflammatory and antioxidant properties that can decrease inflammation and infection and prevent oxidative tissue damage, while taking the physiopathological process of tracheal stenosis formation into consideration.

Erdosteine was developed for the treatment of chronic obstructive bronchitis. The main effects of Erdosteine that cause it to be frequently demanded by clinics are its mucolytic and mucokinetic properties, in addition to its effects in modulating mucus production and viscosity while increasing mucociliary transport. It contains two blocked sulfhydryl groups, one of which, after hepatic metabolization to the active species called Metabolite 1 (Met 1) and opening of the thiolactone ring, becomes available for pharmacologic activity such as free radical scavenging and antioxidant effects [9, 10]. Met 1 has been shown to inhibit nitric oxide, superoxide, and peroxynitrite production in vitro during the respiratory burst of human neutrophils. The possible main mechanism of action of Erdosteine is related to its ability to inhibit some inflammatory mediators and some proinflammatory cytokines that are specifically involved in oxidative stress and in cell membrane damage [11]. Erdosteine, which is a multifactorial drug, prevents the accumulation of free oxygen radicals when their production is accelerated and increases antioxidant cellular protective mechanisms. The final result is a protective effect on tissues, which reduces lipoperoxidation, elastase activity, neutrophil infiltration and cell apoptosis [12, 13]. Throughout the years, the efficacy and tolerability of Erdosteine, which also has known antibacterial and anti-inflammatory activities, have been demonstrated. During the use of Erdosteine, a low incidence of side effects, most of which are gastrointestinal and generally mild, may be observed.

In the present study, based on histological findings, we found that inflammatory cell infiltration in the tracheal surgical area is not inhibited by Erdosteine use. As a secondary effect, this inflammatory cell infiltration causes the increase in free oxygen radicals in the environment, produced by these cells. As a consequence, the increased number of free oxygen radicals that cannot be detoxified lead to increased fibroblast proliferation. We also determined that fibroblast proliferation increased in the Erdosteine group as it did in the control group. Unfortunately, increased fibroblastic activ-

ity is one of the known causes of tracheal stenosis. Whether it is intense inflammatory cell infiltration or increased fibroblast proliferation, they both cause a regionally increased angiogenesis, which also occurred in our study. However, the results we obtained are not consistent with other studies found in the literature. For instance, in their experimental study, Erden et al have created pulmonary fibrosis using Bleomycine and they have investigated the effects of Erdosteine on acute inflammatory changes and fibrosis. In conclusion, they have shown that Erdosteine inhibits acute inflammation by preventing the migration of neutrophils to the inflammation site and blocking the lipid peroxidation that occurs. The authors state that this protective effect of Erdosteine develops due to its removal of free radicals from the environment and its antioxidant activity [12]. In their review, Moretti et al. examined studies from the literature regarding acute injury induced by a variety of pharmacological or noxious agents and concluded that Erdosteine prevents the accumulation of free oxygen radicals when their production is accelerated and increases antioxidant cellular protective mechanisms and protective effects on tissues, which reduces lipid peroxidation, neutrophil infiltration or cell apoptosis mediated by noxious agents [10]. In most of these studies, as targets for tissue injuries mediated by products of oxidative stress, organs with high blood supply such as myocardial tissue, lungs, kidneys and liver have been selected. Thus, it is easier for Erdosteine to achieve adequate levels in the tissues of these organs. In general, the trachea is an organ that has low blood supply, does not have vascular structures that belong to it and it receives its blood supply from surrounding tissues through diffusion. We believe this property of the trachea to be one of the reasons why we did not obtain a positive result with Erdosteine, a potent antioxidant and anti-inflammatory agent. In order for this assumption to be verified, additional studies where tracheal tissue Erdosteine levels are measured are necessary.

In the advanced stages of the wound healing process, remodeling occurs and as a result, new collagen synthesis, granulation and scar tissue formation appear. During this process, collagen deposition begins when fibroblasts enter the wound at 48–72 h post injury. Wound collagen levels reach maximum at 2–3 weeks after injury [1]. Therefore, the results obtained from our study, where Erdosteine did not affect the amount of collagen deposition, may not be valuable due to the short duration of the study. In fact, in order to determine the amount of collagen accumulation in the tracheal surgical area, it seems the length of experimental studies of this type should be approximately at least 3 weeks.

Epithelial regeneration was better in the Erdosteine group. Overall, as a result of this study, with its basis on the idea that epithelial regeneration is an indicator of better wound healing, it was the only emerging positive result obtained with Erdosteine treatment. In fact, we could not completely explain the pharmacological and histological basis of obtaining better epithelial regeneration. However, one of the reasons for this outcome may be the increased fibroblast proliferation leading to activated epithelial cell proliferation and migration. In a study conducted by Nomoto et al regarding this subject, tracheal epithelial cells isolated from the trachea of rats were suspended in a collagenous gel and the collagenous gel with fibroblasts was layered on a collagenous sponge. The grafts of this bioengineered trachea were implanted into tracheal defects of rats. The authors examined the regenerated epithelium in this graft histopathologically and found tracheal fibroblasts to have accelerated epithelial differentiation and proliferation *in vivo* [14]. As a result of their experimental study, Okano et al state that fibroblasts had a stimulatory effect that hastened regeneration of the epithelium in large tracheal defects [15]. As a consequence, the stimulatory effects of fibroblasts on epithelial cell migration, proliferation, and differentiation cause an increase in epithelial regeneration. In summary, a significant increase in epithelial regeneration at the tracheal surgical area affects the results from wound healing positively. Thus, quick epithelialization and wound closure following a tracheal injury may prevent granulation tissue and subsequent fibrosis to a certain degree. However, when we consider increased collagen accumulation and fibroblast proliferation being the main cause of excessive tracheal cicatrisation and tracheal stenosis formation, it can be speculated that induced epithelial regeneration and resulting better wound healing play a small role in preventing tracheal stenosis.

There were some limitations on this experimental study. Some of these consist of the minimal number of rats in our study, the short duration of the experiment and the absence of the use of various doses of Erdosteine. In addition to these, this is a study where the results were obtained through histopathological examination, and biochemical data that may reflect physiopathological changes taking place throughout the tracheal healing period were not examined. Because of this, experiments where more rats are used, include average wound healing time and have longer duration, may show different results, enabling us to understand the possible effects of Erdosteine on tracheal healing in the long-term. To our knowledge, this is the first study with Erdosteine and the tracheal healing process. We believe that future studies that

include groups where researchers look at different doses and time protocols for Erdosteine and possibly different application methods, biochemically determining free oxygen radicals, antioxidant enzymes and lipid peroxidation products in tissue and blood, will increase the value of data obtained from our study.

In conclusion, the present study demonstrates that the severity of pathological changes forming in the tissue after tracheal surgery could not be reduced by the use of Erdosteine. Thus, Erdosteine does not seem to be a useful preventive treatment agent for possible postsurgical tracheal stenosis. On the other hand, this study does not contain information about long-term treatment results. For this reason, further experimental and clinical studies are needed on the effects of Erdosteine in tracheal stenosis.

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